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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/760,274	01/12/2001	John Sinden	GJE-21D2	3086

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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	**PAPER NUMBER**
1632	20

DATE MAILED: 08/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,274	SINDEN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48,57-62,64 and 68-75* is/are pending in the application.

4a) Of the above claim(s) *1-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-62,64 and 68-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/672606 or 09/043061* .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission originally filed on 4-23-03, resent 5-13-03 and 5-30-03, paper number 19, has been entered.

Applicant's arguments filed in paper number 19 have been fully considered but they are not persuasive.

Claims 63 and 65-67 have been canceled. Claims 68-75 have been added. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

This application contains claims 1-48 drawn to an invention nonelected with traverse in Paper No. 8. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 57-62, 64 and 68-75 are under consideration in this office action.

Information Disclosure Statement

The information disclosure statement filed 2-20-01, paper number 3, fails to comply with 37 CFR 1.98(a)(1), because it did not have a PTO-1449 form. Therefore, the IDS filed 2-2-01 cannot be considered.

Specification

The first line of the specification should be updated to reflect that PCT/GB96/02251 has been published as WO 97/10329 on March 20, 1997.

Priority

Claims 57-62, 64 and 68-75 have support in the instant application and parent application 09/043061 (which has the same disclosure). The specification teaches isolating cells from the hippocampus of embryonic day 14, H-2Kb-tsA58 transgenic mice. All cells of the mice are conditionally immortal because they are genetically modified to have a temperature-sensitive oncogene (tsA58) (pg 9, lines 1-15). MHP36 are a clonal cell line "derived" from H-2Kb-tsA58 hippocampal cells (Example 6, pg 24, last 12 lines). The specification teaches MHP15 and MHP36 cells are nestin positive on pg 20, Example 4. The specification teaches administering MHP36 intracerebrally in Example 6, pg 24, and administering MHP15 intracerebrally in Example 8, pg 27. The cells were cultured in permissive conditions (immortal), removed from permissive conditions (non-permissive, allows differentiation) and grafted into rats (para. bridging pg 24-25). The rats are a model for cognitive deficit (pg 25, 1st para. and para. bridging pg 9-10). Pluripotent neuroepithelial cells can be isolated from humans at an equivalent developmental stage, for example at about 8 weeks (pg 13, lines 14-16).

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Great Britain on 9-12-96 (PCT/GB96/02251) and 9-12-95 (9518606.0). A copy of 9518606.0 09/12/1995 and PCT/GB96/02251 were provided in parent application 09/043061. However, the copies were not official priority papers, and applicants have not filed a certified copy of the applications as required by 35 U.S.C. 119(b).

This application repeats a substantial portion of prior Application No. 09/537617, filed 3-29-00, now US Patent 6,569,421, and adds and claims additional disclosure not presented in the prior application. Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78.

It is noted that the declaration filed with the application claimed priority to PCT/GB96/02251 and 9518606.0 but did not claim priority to US applications 09/672,606 or 09/043,061, as in the first line in the specification. A substitute declaration with proper priority claims to 09/672,606, 09/043,061 and PCT/GB96/02251 (now WO 97/10329) and 9518606.0 is required.

Claim Rejections - 35 USC § 112

Written Description

Claims 57-62, 64 and 68-75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

An adequate written description of a method of using human, nestin-positive, neuroepithelial cells for treating a cognitive deficit requires more than a mere statement that the method is part of the invention and reference to a potential method for isolating the cells used in the method. What is required is a description of the human cells capable of treating a cognitive deficit. The specification taught using mouse, pluripotent, nestin-positive, hippocampal neuroepithelial cells to restore cognitive function in rats and suggested isolating pluripotent neuroepithelial cells from humans, for example at about 8 weeks (pg 13, lines 14-16). However, the specification does not teach human cells isolated at about 8 weeks are capable of treating a cognitive deficit. In fact, since the time of filing Gray (August 29, 1999, Philosophical Transactions of the Royal Soc. London, Vol. 354, No. 1388. pg 1407-1421) taught that the window of time in which a tissue is isolated from the fetal brain is essential to obtain the required amount of differentiation and that tissues for treating damage to the hippocampus must be isolated at 15 weeks of gestation (¶ bridging pg 1408-1409, pg 1409, col. 1, lines 4-16). The specification does not teach isolating at 15 weeks of gestation, which is essential to obtain the required amount of differentiation. Villa (2000, Exp. Neurol., Vol. 161, pg 67-84) taught that properties identifying a human neural stem cell are not well understood (pg 81, lines 1-5) and used a working definition of human neural stem cells as those expressing nestin and having the ability to self-renew. Villa taught that the potential of perpetual human neural stem cells required further investigation (pg 82, col. 2, para. 3,

4th sentence). Thus, Villa taught the potential of human neural stem cells expressing nestin and capable of self-renewing remains unknown. Applicants claim human neural stem cells expressing nestin and capable of self-renewal are able to treat cognitive deficit, but have not linked these properties to the ability to treat cognitive deficits. Nor does the specification describe properties of human neural stem cells beyond nestin expression and the ability to self-renew so as to determine cells capable of treating cognitive deficit. Thus, claiming a method of using human, pluripotent, neuroepithelial cells to treat a cognitive deficit without defining the properties required to obtain human cells capable of treating a cognitive deficit is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. It is not sufficient to define the method as requiring human cells having particular biological properties, i.e. expressing nestin and pluripotent, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of human cells capable of restoring cognitive function. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Therefore, applicants did not provide adequate written description for using human, nestin-positive, pluripotent neuroepithelial cells for restoring a cognitive deficit.

Enablement

Claims 57-62, 64 and 68-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a cognitive deficit in a rat caused by a hippocampal lesion comprising administering mouse,

hippocampal, nestin-positive, pluripotent, neuroepithelial cells comprising a vector encoding tsA58 operably linked to the H-2Kb promoter to the hippocampus of the rat such that the cognitive deficit is treated, does not reasonably provide enablement for making or using human, hippocampal, nestin-positive, pluripotent, neuroepithelial cells comprising a vector encoding tsA58 capable of treating a cognitive deficit in a mammal as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The state of the art at the time of filing was such that it is unpredictable how to target particular areas of the brain when transplanting neural cells (Scheffler of record, 1999, Trends in Neurosci, Vol. 22, pg 348-357; see para. bridging pg 354-355).

The hippocampal lesion/water maze model used by applicants is an assay for cognitive deficit (para. bridging pg 9-10). Sinden of record (1997, Neuroscience, Vol. 81, pages 599-608) taught for transplanted neural cells to restore performance in water maze tests, the cells must be CA1 cells derived from the hippocampus and highly specific to the damaged CA1 tissue (page 601, paragraph bridging columns 1 and 2). For example, CA1 cells are effective, but CA3 cells derived from the hippocampus or cells derived from other portions of the brain are not effective (page 601, sentence bridging columns 1 and 2).

Applicants claim human neural stem cells expressing nestin and capable of self-renewal are able to treat cognitive deficit, but have not linked cells having such a phenotype to the ability to treat cognitive deficits.

The specification teaches obtaining hippocampal, pluripotent neuroepithelial cells from H-2Kb-tsA58 transgenic mice, culturing the cells in "permissive" conditions (immortal), removing the cells from "permissive" conditions (cells begin to differentiate) and transplanting the cells to the CA1 area of rats with damaged CA1 tissue. The rats receiving H-2kb-tsA58 cells showed improved performance as compared to the ischemia control animal and an equivalent performance as compared to a sham control animal in the water maze test (Example 5, pg 22; pg 23, line 8; Fig. 9). The specification also teaches obtaining MHP36, a clonal cell line derived from the H-2Kb-tsA58 mouse, hippocampal neuroepithelial cells, which showed similar results (Example 6, pg 24, Fig. 10). The mouse MHP36 cell line is nestin-positive as claimed (Example 4, pg 21, lines 1-6). The specification states the cells of the invention can be isolated from humans at an equivalent developmental stage, for example at about 8 weeks (pg 13, lines 14-16). However, the specification does not teach human cells isolated at about 8 weeks are capable of treating a cognitive deficit.

In fact, since the time of filing Gray (August 29, 1999, Philosophical Transactions of the Royal Soc. London, Vol. 354, No. 1388. pg 1407-1421) taught that the window of time in which a tissue is isolated from the fetal brain is essential to obtain the required amount of differentiation required for using the cells in transplantation treatments. Gray states specifically that cells used to treat damage to the hippocampus must be isolated at 15 weeks of gestation (¶ bridging pg 1408-1409, pg 1409, col. 1, lines 4-16). The specification does not teach isolating at 15 weeks of gestation, which is essential to obtain the required amount of differentiation need to treat a cognitive deficit. Villa

(2000, Exp. Neurol., Vol. 161, pg 67-84) taught that properties identifying a human neural stem cell are not well understood (pg 81, lines 1-5) and used a working definition of human neural stem cells as those expressing nestin and having the ability to self-renew. Villa taught that the potential of perpetual human neural stem cells required further investigation (pg 82, col. 2, para. 3, 4th sentence). Thus, Villa taught the potential of human neural stem cells expressing nestin and capable of self-renewing remains unknown.

Thus, the specification does not teach human, pluripotent, hippocampal, nestin-positive neuroepithelial cells capable of treating a cognitive deficit as claimed or correlate mouse cells having such an ability to human cells. The specification described isolating human cells for treating cognitive deficit at 8 weeks of gestation, which is contrary to the teachings since the time of filing of Gray (1999) who taught human cells for treating cognitive deficit must be isolated at week 15 and that the time of isolating cells for brain transplantation is essential to obtaining the desired effect. It would have required one of skill undue experimentation to determine human, nestin-positive, pluripotent, hippocampal, neuroepithelial cells capable of treating cognitive deficit or for using human, nestin-positive, pluripotent neuroepithelial cells for restoring a cognitive deficit.

While the specification states human cells are obtained from a stage equivalent to day 14 or 15 in mice, i.e. about 8 weeks of gestation in humans, the declaration by Dr. Sinden filed 10-7-02, paper number 13, states human pluripotent neuroepithelial cells capable of restoring cognitive function were isolated at 12 weeks of gestation. 12

weeks of gestation in humans is not equivalent to day 14 or 15 of gestation in mice as described in the specification. Secondly, the human cells were isolated from the cortex and not the hippocampus as taught in the specification. Thirdly, the mouse cells were obtained from transgenic mice whose genomes comprise DNA encoding the temperature sensitive gene (tsA58). However, the specification does not teach how to make equivalent cells from transgenic humans, how to incorporate a temperature sensitive gene into the genome of human, pluripotent, neuroepithelial cells or how to obtain levels of tsA58 expression found in mouse MPH36 cells required for temperature sensitivity using transfection methods in human cells. Finally, according to the declaration, the human cells that treated cognitive deficit expressed musashil, which is not taught in the specification. As such, the human equivalent of the mouse, nestin-positive, pluripotent neuroepithelial cells does is not adequately taught in the specification as originally filed because more information than given in the specification would have been required for one of skill to obtain a human cell encoding tsA58 having the ability to restore cognitive function found in MHP36. Therefore, applicants did not provide adequate guidance for one of skill in the art at the time of filing to obtain human, nestin-positive, pluripotent neuroepithelial cells claimed capable of the sole disclosed use for such cells, restoring cognitive function. It would have required one of skill undue experimentation to determine that musashil expression, isolation from the cortex and 12 weeks of gestation were required to obtain the human cells claimed capable of treating a cognitive deficit as claimed. Therefore, the specification did not enable one of skill in the art at the time of filing to use human cells to treat a cognitive deficit as claimed.

In addition, expression of the tsA58 must be inducible, e.g. under the control of an inducible promoter. The specification taught using the interferon-inducible H-2Kb promoter but did not teach using constitutive promoters as encompassed by the claims. It would have required one of skill undue experimentation to determine how to use cells comprising DNA encoding tsA58 as claimed that was not controlled by an inducible promoter such that the cells differentiated upon being transplanted into the hippocampus.

Indefiniteness

The rejection of claims 57-67 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn because the claims have been canceled.

35 USC § 103

The rejection of claims 57-60, 62 and 65-67 over Netto taken with Renfranz has been withdrawn because the claims have been canceled and because new claims 68-75 require the cells are human cells (incorporating the limitation of claim 63). Netto taken with Renfranz did not teach the cells were human cells.

The rejection of claims 57-62 and 65-67 over Netto taken with Renfranz and Rashid-Doubell and White has been withdrawn because the claims have been canceled and because new claims 68-75 require the cells are human cells (incorporating the

limitation of claim 63). Netto taken with Renfranz, Rashid-Doubell and White did not teach the cells were human cells.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 57-62, 64 and 68-75 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,569,421 in view of Snyder of record (US Patent 5,958,767, Sept. 28, 1999). Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of '421 require treating a cognitive deficit in a mammal caused by brain damage comprising administering pluripotent cells into a damaged mammalian brain, wherein said damage is primarily in one hemisphere and said administration is into the brain hemisphere contralateral to the brain hemisphere containing the primary site of damage, wherein the pluripotent cells are hippocampal mouse cells comprising a gene encoding the tsA58 mutant of the SV40 large T antigen

under the control of the H-2Kb promoter, wherein the cells are capable of differentiating into neural cells, and wherein the cells are administered in an amount effective to improve cognitive deficit. The claims of '421 do not require the cells are human and nestin positive cells or that the cells are administered to a site of damaged hippocampal tissue as required in the instant application. However, the cells of '421 inherently express nestin because they are pluripotent, hippocampal, neuroepithelial cells. In addition, Snyder taught human pluripotent neuroepithelial cells that were transplanted into the area of brain damage to treat cognitive function. It would have been obvious to one of skill in the art at the time of filing to make and use human cells as taught by Snyder in the method of '421 and to administer the cells directly to the damaged area of the brain to increase the amount of therapeutic cells in the damaged area.

Thus, Applicants' claimed invention, as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Claims 57-62, 64 and 68-75 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application Nos. 09/672,606, 10/342692 and 10/376119. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims would anticipate the claims of '606, '692 and '119.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

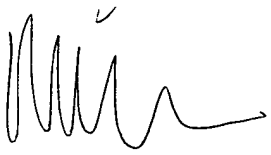
Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER